P.D:4/06/1994 P: 1432/1433 (2)

illness, deteriorated rapidly, and died. Necropsy was not performed. We do not feel that she died of MDR-TB.

Improved survival for patients with MDR-TB and AIDS may be achievable with early diagnosis and treatment.[4,5] However, the optimum long-term arrangement for patients with MDR-TB and AIDS is unknown. Although stabilisation of such patients may be possible, cure may not be. Because many patients remain intermittently smear and culture positive for months, return to their former residences, if they house other HIV-infected persons, or to a congregate setting, is precluded. Our patients spent 594 days in respiratory isolation. The cost of the hospital admission exceeded $445 000; the cost to the patient in loss of dignity and hope cannot be measured. Public health policy should be developed to include alternative sites for the long-term care of survivors of AIDS and MDR-TB.

Victoria Sharp, Philippe Chiliade, Kent A Sepkowitz
Spellman Center, St Clare's Hospital and Health Center, New York; and Memorial Sloan-Kettering Cancer Center, New York Hospital-Cornell Medical Center, New York, NY 10021, USA

1 Bloch AB, Cauthen GM, Onorato IM, et al. Nationwide survey of drug-resistant tuberculosis in the United States. *JAMA* 1994; 271: 665–71.
2 Goble MJ, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh RC. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993; 328: 527–32.
3 Centers for Disease Control. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons: Florida and New York. *MMWR* 1991; 40: 585–91.
4 Lockhart B, Sharp V, Squires KE, Chopra A, Sepkowitz KA. Improved outcome of MDR-TB in patients receiving a five or more drug initial therapy. IXth International Conference on AIDS, Berlin, Germany, June 7-11, 1993 (abstr PO-B07-1167).
5 Edlin BR, Arroe LS, Gneco MH, Williams J, Schneider N, Gilligan ME. Recognition and treatment of primary multidrug-resistant tuberculosis (MDRTB) in HIV-infected patients. IXth International Conference on AIDS, Berlin, Germany, June 7-11, 1993 (abstr WS-BO9-6).

Intravenous fluids and parageustia

SIR—Emergency admission with a low intestinal obstruction gave me a patient's view of a hospital. I told the tea ladies while recovering from surgery that their tea, coffee, cocoa, and water were so unpalatable as to be virtually undrinkable, to which they replied that all patients on intravenous fluids lost their sense of taste but that it would return three days after my drip was withdrawn. I had assumed that it was the effect of the anaesthetic and operation—as did the nurses. The catering staff assured me that it was only patients on drips who reacted thus, even those who had not had anaesthesia.

52 hours after withdrawal of intravenous fluids my parosmia ended and the ward no longer had a neglected-laundry odour. I suggest that at a certain point the intravenous saline alters the osmotic balance in the oral cavity and nasopharynx, affecting the taste buds and olfactory end organs and thus causing reversible parageusia and parosmia. Since few seem to be aware of this physiological reaction to intravenous fluids (despite the fact that such fluids have been used for about a century) it should be more widely reported.

Intravenous-fluid parageusia has pertinent implications. In maternity work, bonding between baby and mother could be damaged if either is given intravenous fluids. In puerperal depression it might add to distress. It can affect patients being treated for bulimia and anorexia. The reaction might be used when treating tobacco addicts, to help them reject their cigar, cigarette, or pipe. It could account for the ending of their addiction by smokers who undergo surgery. Perhaps it explains criticism of hospital catering.

S W Vivian Davies
Pen Y Nant, 4 Tregew Road, Flushing, Cornwall TR11 5TG, UK

XP-002140637

Protection against Alzheimer's disease with apoE ε2

SIR—An association between the apolipoprotein ε4 allele and Alzheimer's disease (AD) has been observed in many studies.[1] Increased dosage of the ε4 allele appears to decrease the age of onset of AD[1] and may increase the β-amyloid plaque burden in AD brains[2] which suggest the association has biological importance. There is some evidence for a negative association, or protective effect, of the ε2 allele in sporadic cases of AD.[3] We report further evidence for this effect.

93 patients with sporadic AD (mean [SD] age 75 [8]) and 67 normal controls from the same ethnic background (mean age 77 [10]) were recruited through the patient registry of the Washington University Alzheimer's Disease Research Center. Individuals were genotyped at the apoE locus with a standard method. We found an increase in ε4 allele frequency in patients compared with controls (χ^2=7·75, 1 degree of freedom, one-tailed p=0·0027) and a decrease in ε2 allele frequency (Fisher's exact test, one-tailed p=0·0048) whereas the decreased frequency of ε3 in the patient group was not significant. Allele ε2 conferred a strong protective effect in our sample, with the odds ratio for AD for subjects possessing this allele being 0·08 (95% CI 0·01–0·69). In contrast, the protective effect of the ε3 allele was less marked (odds ratio for possessing at least one ε3 allele 0·16), and not significant (95% CI 0·18–1·37).

The strength and specificity of the effect of the ε2 allele suggest that the cause is not simply the absence of an ε4 allele but that the ε2 mutation confers protection against AD when compared with the ancestral apoE ε3 allele. The observation of opposite effects on the risk for AD by two different alleles at the apoE locus provides additional support for the direct involvement of apoE in AD pathogenesis.

The pathogenic mechanism of apoE in AD is not fully understood but may be mediated by binding to soluble β-amyloid.[4] The ε4 allele has been shown in vitro to have a higher binding affinity for β-amyloid than ε3. If this explains the predisposing effect of the ε4 isoform then we would expect apoE ε2 to have a lower affinity for β-amyloid. We would also predict that individuals with ε2/ε3 and ε2/ε2 genotypes would have lower β-amyloid plaque densities than either ε3 homozygotes or individuals with an apoE ε4 allele. Since AD is an important cause of morbidity in the elderly, the protective effect of apoE ε2 on risk for AD may explain the recently reported positive association of apoE ε2 with

Genotype	Controls (n=67)	Sporadic AD (n=93)
ε2/ε2	0	0
ε2/ε3	8	1
ε2/ε4	0	0
ε3/ε3	39	46
ε3/ε4	19	38
ε4/ε4	1	8
Allele frequency		
ε2	0·060	0·005
ε3	0·783	0·705
ε4	0·157	0·290

Table: **apoE allele frequencies in sporadic AD cases and non-demented controls**

BNSDOCID <XP_____2140637A__I_>

human longevity.[1] Understanding the role of apoE ε2 in protecting against the risk of AD should contribute greatly toward the development of treatments and preventive strategies for AD.

This work was supported by a grant from the NIA (AG05681). AG is the recipient of an NIA career development award (AG00634-01) and NC is a Wellcome Trust Research Fellow.

Christopher Talbot, Corinne Lendon, Nick Craddock, Shantia Shears, John C Morris, Alison Goate
Departments of Psychiatry and Neurology, Washington University School of Medicine St Louis MO 63117, USA

1 Corder E, Saunders A, Strittmatter W, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993, 261: 921-23
2 Schmechel D, Saunders A, Strittmatter W, et al. Increased amyloid b-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer's disease. *Proc Natl Acad Sci USA* 1993, 90: 9649-53.
3 Chartier-Harlin M-C, Parfitt M, Legrain S, et al. Apolipoprotein E e4 allele as a major risk factor for sporadic early and late-onset forms of Alzheimer's disease: analysis of the 19q13 2 chromosomal region. *Hum Mol Genet* 1994; 3: 569-74.
4 Strittmatter WJ, Weisgraber KH, Huang DY, et al. Binding of human apolipoprotein E to synthetic amyloid β-peptide: isoform specific effects and implications for late-onset Alzheimers disease. *Proc Natl Acad Sci USA* 1993, 90: 8098-102.
5 Schachter F, Faure-Delanef L, Guenot F, et al Genetic associations with human longevity at the ApoE and ACE loci. *Nat Genet* 1994; 6: 29-32

Fulminant hepatitis C virus infection

SIR—Transfusion-associated hepatitis C virus (HCV) infections have been reduced with the introduction of serological testing for HCV. However, even second-generation HCV assays enabling the detection of structural and nonstructural viral proteins lack the sensitivity to detect viraemia in all cases.[1] Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analogue that has been shown to be effective in the treatment of hairy-cell leukaemia with complete remission rates between 75% and 85%[2,3] and few side-effects. Little is known about possible interactions with liver disease, but an increase in alanine aminotransferase (ALT) has not been reported.

We report a 51-year-old female patient with hairy-cell leukaemia who received three units of packed red cells 18 days before initiation of treatment with cladribine (0·1 mg/kg daily). Liver function tests were normal before treatment. Treatment, however, had to be stopped after 3 days because jaundice and grade 1 encephalopathy developed. On day 10, ALT concentrations peaked at sixty times normal, encephalopathy progressed to grade 2, and prothrombin fell to 25% (normal >70%). By day 25, ALT had returned to normal and the patient subsequently made a complete recovery.

Cladribine caused a 7-day episode of neutropaenia and rapid clearing of hairy cells from peripheral blood within a week. A substantial fall in ALT values followed the drop in peripheral helper (CD4) and suppressor (CD8) T cells with a delay of 6 days. 2 weeks later, the liver disease flared up but the CD4 and CD8 counts returned to normal (figure). The nadir of the T cells (CD3) and CD16 cells (100/μL) on day 8 correlated with the peak of ALT. During the time of increased ALT, the patient had a normal T-cell ratio in peripheral blood. HCV antibodies tested repeatedly positive after day 50 (Abbott Diagnostics, second generation enzyme-linked immunosorbent assay). Because the patient had normal aminotransferase values but remained HCV-RNA positive for more than 3 months (nested polymerase

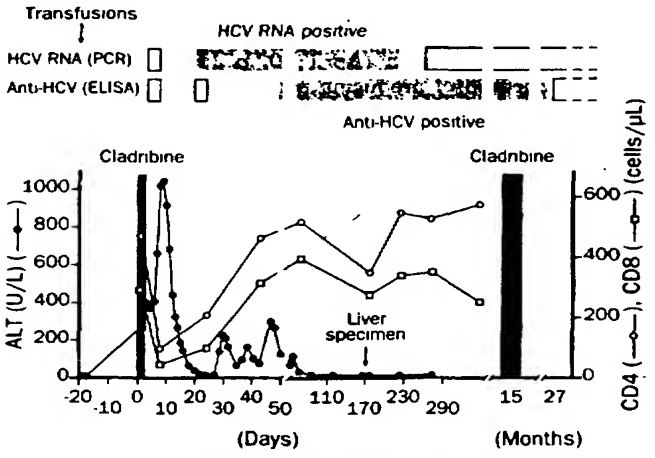

Figure: **Clinical course of hepatitis C infection**
Open bars indicate negative results and filled bars indicate when serum was positive. Days with cladribine infusions are marked by dark vertical bar.

chain reaction [PCR] primers from the 3' non-coding region), liver biopsy was carried out 5 months after therapy to rule out chronic liver disease. Histology showed normal liver architecture without inflammation, and HCV RNA became undetectable on repeated testing after 9 months.

After 3 months, bone marrow examination showed partial remission with 12% hairy-cell infiltration. However, the number of hairy cells in the bone marrow rose to 20% after 1 year. A course of 7 days' treatment with cladribine (0·1 mg/kg daily) was given without any increase in ALT 15 months after the first course. This second treatment resulted in complete remission of the hairy-cell leukaemia. HCV antibodies were negative 9 months after the second course of cladribine.

This case is remarkable for several reasons. First, a fulminant increase in ALT occurred during cladribine therapy yet had a benign course. During the second course of treatment with cladribine, there was no liver reaction. This, together with seroconversion, would suggest that fulminant hepatitis C and not cladribine, was responsible for the increase in ALT during the first course of cladribine. Second, the rapid return to normal of ALT correlated with marked changes in the number of CD4 and CD8 cells. Third, the patient tested negative for HCV RNA early in the hepatitic phase.

Our observations indicate that cladribine may not be detrimental in hepatitis C. The short course of hepatitis C under these conditions could mean either that the reduction in cytotoxic T cells is related to the liver disease, underscoring the role of the immune system in HCV, or that cladribine has some direct antiviral effect. The early negative results for HCV RNA by PCR stress the need for repeated testing in fulminant HCV.

M Schirmer, W Vogel, J Thaler, K Grünewald, F Umlauft, F Geisen, U Zilian, G Konwalinka
Department of Internal Medicine, Innsbruck University, A-6020 Innsbruck, Austria

1 Aach RD, Cladd ES, Hollinger FB, et al. Hepatitis C virus infection in post-transfusion hepatitis. *N Engl J Med* 1991, 325: 1325-29.
2 Beutler E. Cladribine (2-chlorodeoxyadenosine). *Lancet* 1992; 340: 952-56.
3 Piro LD, Carrera CJ, Carson DA, Beutler E. Lasting remissions in hairy-cell leukaemia induced by a single infusion of 2-chlorodeoxyadenosine. *N Engl J Med* 1990; 322: 1117-21.

BNSDOCID <XP_____2140637A__I_>